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☐ **1:** *190080 Links
V-MYC AVIAN MYELOCYTOMATOSIS VIRAL ONCOGENE HOMOLOG; MYC
Gene map locus 8q24.12-q24.13

☐ **2:** *600999 Links
MYC-ASSOCIATED ZINC FINGER PROTEIN; MAZ
Gene map locus 16p11.2

☐ **3:** *604899 Links
PREFOLDIN 5; PFDN5

☐ **4:** *602310 Links
RNA-BINDING MOTIF PROTEIN, SINGLE STRAND-INTERACTING, 1; RBMS1

☐ **5:** *603015 Links
TRANSFORMATION/TRANSCRIPTION DOMAIN-ASSOCIATED PROTEIN; TRRAP
Gene map locus 7q21.2-q22.1

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JUNCTION PLAKOGLOBIN; JUP
Gene map locus 17q21

☐ **7:** *600382 Links
MYC PROMOTER-BINDING PROTEIN

☐ **8:** #150699 Links
LEIOMYOMA, UTERINE

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PEROXIREDOXIN 3; PRDX3
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ADENOMATOUS POLYPOSIS OF THE COLON; APC
GARDNER SYNDROME, INCLUDED; GS, INCLUDED
Gene map locus 5q21-q22, 1p34.3-1p32.1

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CYSTEINE- AND GLYCINE-RICH PROTEIN 1; CSRP1
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☐ **17:** #113970 Links
BURKITT LYMPHOMA; BL
Gene map locus 8q24.12-q24.13

☐ **18:** *606535 Links
MYC-BINDING PROTEIN; MYCBP
Gene map locus 1p33-p32.2

☐ **19:** *606355 Links
DEAD/H BOX 18; DDX18

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GLUCOCORTICOID RECEPTOR DNA-BINDING FACTOR 1; GRLF1
Gene map locus 19q13.2-q13.4

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V-MYC AVIAN MYELOCYTOMATOSIS VIRAL ONCOGENE HOMOLOG; MYC

Alternative titles; symbols

ONCOGENE MYC
AVIAN MYELOCYTOMATOSIS VIRAL ONCOGENE HOMOLOG
PROTOONCOGENE HOMOLOGOUS TO MYELOCYTOMATOSIS VIRUS

Gene map locus 8q24.12-q24.13

TEXT

Sequences of the MYC oncogene have been highly conserved throughout evolution, from Drosophila to vertebrates (Shilo and Weinberg, 1981). Persson and Leder (1984) showed that the product of the MYC gene has a molecular weight of 65,000, is located predominantly in the nucleus, and binds to DNA.

Leder (1982) described in situ hybridization observations suggesting that the MYC locus is on chromosome 8 near 8q24, the breakpoint in Burkitt lymphoma translocations. Collins and Groudine (1982) found that the normal human homolog of the avian myc oncogene was present in multiple copies in the DNA of a malignant promyelocyte cell line derived from the peripheral blood of a patient with acute promyelocytic leukemia. Other human onc genes were not amplified. By the Southern blotting technique applied to somatic cell hybrids, Dalla-Favera et al. (1982) showed that the MYC gene is on chromosome 8. When hybrids between rodent cells and human Burkitt lymphoma cells were analyzed, they could show that the MYC gene is on the part of chromosome 8 (8q24-qter) that is translocated to 2, 14, or 22. Several MYC-related sequences may be pseudogenes. Taub et al. (1982) also mapped the MYC gene to 8q24 and found that in 2 Burkitt cell lines MYC was translocated into a DNA restriction fragment that also encodes the immunoglobulin mu chain gene. In a mouse plasmacytoma, the MYC gene was translocated into the immunoglobulin alpha switch region. Observations such as those of Alitalo et al. (1983) indicate that the same oncogene which in one chromosomal change or rearrangement produces one specific neoplasm results, when altered in a different way, in a different neoplasm. Alitalo et al. (1983) found that the MYC gene, which is involved by translocation in the generation of Burkitt lymphoma, is amplified, resulting in homogeneously staining chromosomal regions (HSRs) in a human neuroendocrine tumor cell line derived from a colon cancer. The HSR resided on a distorted X chromosome; amplification of MYC had been accompanied by translocation of the gene from its normal position on 8q24. Maguire et al. (1983) found that Burkitt and non-Burkitt lymphomas with either an 8;14 or an 8;22 translocation expressed 2- to 5-fold more MYC-specific RNA than B-cell lines without a translocation. Tumor cell lines of American origin with a translocation of either type expressed similar amounts of MYC-specific RNA. Tumor cell lines of African origin contained slightly higher levels of MYC-specific RNA than American lines, but the level did not

correlate with absence or presence of Epstein-Barr virus (EBV). No MOS-related transcripts were found in these tumors. In Burkitt lymphomas bearing the 8;14 translocation, the MYC gene is translocated to a heavy chain switch recombination region (mu or alpha). See Adams et al. (1983). By fluorescence in situ hybridization in combination with R banding, Takahashi et al. (1991) refined the assignment of MYC to 8q24.12-q24.13, distal to fragile site fra(8)(q24.11).

The 14q marker in Burkitt lymphoma was first found by Manolov and Manolova (1972). Zech et al. (1976) showed that the extra chromosomal material joined to the end of one chromosome 14 is derived from the distal part of 8q. Bernheim et al. (1981) found either 2;8 or 8;22 translocation in about 10% of cases. The translocations separate the MYC gene from its normal promoter and 5-prime regulatory machinery, and place it under some regulatory element associated with the immunoglobulin gene. By hybrid cell studies of mouse plasmacytoma cells and Burkitt lymphoma cells, Nishikura et al. (1983) showed that cells containing the MYC gene on a translocation chromosome expressed high levels of human specific MYC transcripts whereas hybrid cells containing the untranslocated MYC gene on the normal chromosome did not contain such MYC mRNA. Usually in t(8;14) translocations, the MYC gene is translocated to 14q. When the break occurs between the MYC first and second exons, both segments are transcriptionally active. Croce et al. (1983) studied somatic cell hybrids between mouse myeloma cells and a Burkitt lymphoma human cell line with a t(8;22) chromosome translocation. The MYC gene was found to remain on chromosome 8q+; the normal chromosome 8 remains transcriptionally silent. The lambda constant region is translocated 3-prime to the MYC oncogene. Yokota et al. (1986) concluded that alterations are found in oncogenes MYC, HRAS, or MYB in more than one-third of human solid tumors. Amplification of MYC was found in advanced widespread tumors and in aggressive primary tumors. Apparent allelic deletions of HRAS and MYB could be correlated with progression and metastasis of carcinomas and sarcomas.

Erikson et al. (1986) studied 2 patients with a t(8;14)(q24;q11) chromosome translocation. In 1, rearrangement was detected in a region immediately 3-prime to the MYC locus. In the second, the breakpoint in the chromosome 14 occurred between genes for the variable and constant regions of the T-cell receptor alpha chain (186880). The constant region locus had translocated to a region more than 38 kb 3-prime to the MYC gene, yet as was shown by the study of hybrids between the human cells and mouse cells, only the hybrids carrying the 8q+ chromosome expressed MYC. Thus, deregulation of the MYC locus can occur not only with translocation of the heavy chain locus or one or the other light chain locus to chromosome 8 but also with translocation of the TCRA locus. The involvement of the MYC oncogene in translocations is the prototype in the relationship between chromosomal abnormalities and oncogenes.

Heim and Mitelman (1987) counted a total of 83 bands that have been found to be specifically involved in primary structural chromosome rearrangements in human cancer. They compared the distribution of these breakpoints with the chromosomal sites of 26 cellular oncogenes which had to that time been mapped to individual bands in the human genome. Nineteen of the 26 oncogenes were located in cancer-associated bands. This clustering is statistically significant ($p = 0.0000012$). They pointed out that cancer may be inflated by errors of karyotype interpretation. Furthermore, it appears that only 1 of the 2 breakpoints in cancer-specific translocations is the site of an oncogene, so that the number of cancer-associated breakpoints that are found to contain oncogenes should theoretically approach 50% of the total. Mitelman (1985) provided a useful catalog of chromosome aberrations in cancer. Duesberg (1987) suggested that cellular cancer genes are not activated oncogenes but rather the result of rare truncations and illegitimate recombinations that alter the germline configuration of cellular genes. See review by Cole (1986). Since MYC is proximal to the thyroglobulin gene (TG; 188450), which is located in the segment 8q24.2-q24.3, MYC may be located in band 8q24.1.

EBV is stably maintained and partially expressed in Burkitt lymphoma and in nasopharyngeal carcinoma. Latently infected cells usually contain multiple episomal copies of nonintegrated viral DNA. In 2 Burkitt cell lines, Henderson et al. (1983) showed that EBV was also integrated into a chromosome, but different chromosomes--nos. 1 and 4. The persistence of EBV in latently infected cells over years of active cell replication may be explained by integration. It is noteworthy that the site of integration is removed from those involved in the translocation. 'The simplest model to explain EBV association with Burkitt tumors is that EBV induces B-cell proliferation and thereby provides enhanced opportunity for chromosomal translocation and malignant degeneration' (Henderson et al., 1983).

Morse et al. (1988) found an MYC rearrangement in a breast carcinoma due to insertion of a LINE-1 (L1) element. (Mobile genetic elements are an important source of genetic variability in both prokaryotes and eukaryotes, including Drosophila, yeast, and mouse. At least 10% of the human genome is composed of repetitive retrotransposon-like sequences including short, interspersed Alu sequences, nonviral retrotransposon-like LINE-1 sequences, and the long terminal repeat (LTR)-containing THE-1 elements. Factor VIII mutations due to L1 insertions have been reported (306700) and an Alu transposition event has been found in human lung carcinoma cells (Lin et al., 1988). The RTVL-H family of human endogenous retrovirus-like elements has approximately 1,000 intact members and a similar number of solitary LTRs in the haploid genome. The intact RTVL-H sequences are 5.8 kb long, have 5-prime and 3-prime LTRs and have some segments of sequence similarity to mammalian retroviruses in the putative gag and pol regions. Mager and Goodchild (1989) demonstrated DNA variation in 2 sibs representing a deletion due to homologous recombination between the 5-prime and 3-prime LTRs of a RTVL-H sequence.) Specific types of human papillomavirus (HPV), mostly HPV type 16 (HPV16) and type 18 (HPV18), are associated with genital carcinomas such as those of the cervix and their noninvasive precursors (167959, 167960). In intraepithelial neoplasia, HPV DNA is detected most commonly as episomal molecules, whereas it is found integrated in the cell genome in the majority of invasive carcinomas. By chromosomal in situ hybridization experiments, Couturier et al. (1991) determined the localization of integrated HPV16 or HPV18 genomes in genital cancers. In 3 cancers, HPV sequences were located in band 8q24.1, which contains the MYC gene, and in 1 cancer, HPV sequences were located in band 2p24, which contains the NMYC gene (164840). In 3 of the 4 cases, the protooncogene located near integrated viral sequences was found to be structurally altered and/or overexpressed.

Atchley and Fitch (1995) described phylogenetic analyses for 45 MYC protein sequences. A gene duplication early in vertebrate evolution produced the c-myc lineage and another lineage that later gave rise to the N- and L-myc lineages by another gene duplication. Evolutionary divergence in the MYC gene family corresponded closely to the known branching order of the major vertebrate groups. The closely related dimerization partner protein MAX (154950) exhibited significantly less variability than MYC. Atchley and Fitch (1995) suggested a reduced variability in MAX stems from natural selection acting to preserve dimerization capability with products of MYC and related genes.

Cell proliferation is regulated by the induction of growth promoting genes and the suppression of growth inhibitory genes. Malignant growth can result from the altered balance of expression of these genes in favor of cell proliferation. Induction of the transcription factor MYC promotes cell proliferation and transformation by activating growth-promoting genes, including the ornithine decarboxylase (ODC1; 165640) and CDC25A (116947) genes. Lee et al. (1997) showed that MYC transcriptionally represses the expression of the growth arrest gene (GAS1; 139185). A conserved MYC structure, MYC box 2, is required for repression of GAS1 and for MYC induction of proliferation and transformation, but not for activation of ODC1.

The MYC protein activates transcription as part of a heteromeric complex with MAX. However, cells

transformed by MYC are characterized by the loss of expression of numerous genes, suggesting that MYC may also repress gene expression. By searching for proteins that may mediate gene repression by MYC, Peukert et al. (1997) identified ZNF151 (604084), which they called MIZ1 for 'MYC-interacting zinc finger protein-1.' MIZ1 interacts specifically with the helix-loop-helix domain of MYC and NMYC. The predicted MIZ1 protein contains a POZ (poxvirus and zinc finger) domain, which appears to act as a negative regulatory domain for transcription factor function, and 13 zinc finger domains. MIZ1 has a potent growth arrest function and can bind to and transactivate the adenovirus major late and cyclin D1 (CCND1; 168461) promoters. Interaction between MIZ1 and MYC overcomes MIZ1-induced growth arrest, inhibits MIZ1 transactivation, induces MIZ1 nuclear sequestration, and renders MIZ1 insoluble in vivo. These effects depend on the integrity of the POZ domain of MIZ1. Peukert et al. (1997) suggested that MYC inhibits gene transcription by activating the latent inhibitory functions of the MIZ1 POZ domain.

Grandori et al. (1996) identified DDX18 (606355) as a direct in vivo target of Myc and Max and hypothesized that Myc may exert its effects on cell behavior through proteins that affect RNA structure and metabolism.

He et al. (1998) provided a molecular framework for understanding the previously enigmatic overexpression of MYC in colorectal cancers. Inactivating mutations in the adenomatous polyposis coli gene (APC; 175100), found in most colorectal cancers, cause aberrant accumulation of beta-catenin (CTNNB1; 116806), which then binds T-cell factor 4 (TCF4; 602228), causing increased transcriptional activation of unknown genes. He et al. (1998) showed that the MYC oncogene is a target in this signaling pathway. They showed that expression of MYC is repressed by wildtype APC and activated by beta-catenin, and that effects are mediated through TCF4 binding sites in the MYC promoter.

Wu et al. (1999) demonstrated that the MYC protein represses the expression of ferritin-H (134770), which sequesters intracellular iron, and stimulates the expression of iron regulatory protein-2 (IRP2; 147582), which increases the intracellular iron pool. Downregulation of ferritin-H expression was required for cell transformation by c-myc. Wu et al. (1999) further demonstrated that the downregulation of ferritin-H expression was independent of c-myc-induced changes in cell cycle activity. The authors concluded that this function for c-myc is consistent with observations that iron chelation leads to growth arrest.

Contrary to the previous belief that MYC is wildtype in both types of tumors, Bhatia et al. (1993) found that 65% of 57 Burkitt lymphomas and 30% of 10 mouse plasmacytomas exhibited at least 1 amino acid substitution. These mutations were apparently homozygous in all Burkitt lymphoma cell lines tested and in 2 tumor biopsies, implying that the mutations often occur before MYC/IG translocation. In the mouse plasmacytomas, only the mutant myc allele was expressed, indicating a functional homozygosity with occurrence of mutations at the translocation. Many of the observed mutations were clustered in regions associated with transcriptional activation and apoptosis, and in the Burkitt lymphomas, they frequently occurred at sites of phosphorylation, suggesting that the mutations had a pathogenetic role. Most of the mutations observed were clearly not polymorphisms, for reasons in addition to the large number of different mutations observed: 1) a high proportion were missense mutations; 2) most tumors contained multiple mutations; and 3) each tumor had a unique pattern of mutations.

Wu et al. (1999) demonstrated direct activation of telomerase by MYC. Telomerase is the ribonuclear protein complex expressed in proliferating and transformed cells, in which it preserves chromosomal integrity by maintaining telomere length. MYC activates telomerase by inducing expression of its catalytic subunit, telomerase-reverse transcriptase (TERT; 187270). Telomerase complex activity is dependent on TERT, a specialized type of reverse transcriptase. Wu et al. (1999) showed that TERT is a

target of MYC activity and identified a pathway linking cell proliferation and chromosome integrity in normal and neoplastic cells.

Wang et al. (2000) demonstrated that TERT-driven cell proliferation is not genoprotective because it is associated with activation of the MYC oncogene. Human mammary epithelial cells, which normally stop dividing in culture at 55 to 60 population doublings (PDs), were infected with human TERT retrovirus at PD40 and maintained until PD250. Wang et al. (2000) then tested whether telomerase activity was essential for the immortalized phenotype by excising the TERT retrovirus at PD150 using Cre recombinase. The resulting cells were maintained for at least another 20 population doublings, and no decline in growth rates in either pooled cells or individual clones was observed. Ectopic expression of MYC was found to be upregulated between 107 and 135 population doublings. Wang et al. (2000) suggested that under standard culture conditions, extension of lifespan by telomerase selects for MYC overexpression in human mammary epithelial cells.

MYC induces transcription of the E2F1 (189971), E2F2 (600426), and E2F3 (600427) genes. Using primary mouse embryo fibroblasts deleted for individual E2f genes, Leone et al. (2001) showed that MYC-induced S phase and apoptosis requires distinct E2F activities. The ability of Myc to induce S phase was impaired in the absence of either E2f2 or E2f3 but not E2f1 or E2f4 (600659). In contrast, the ability of Myc to induce apoptosis was markedly reduced in cells deleted for E2f1 but not E2f2 or E2f3. The authors proposed that the induction of specific E2F activities is an essential component in the MYC pathways that control cell proliferation and cell fate decisions.

In addition to immunoglobulin V genes, the 5-prime sequences of BCL6 (109565) and FAS (TNFRSF6; 134637) are mutated in normal germinal center B lymphocytes. Genomic instability promotes tumorigenesis through defective chromosome segregation and DNA mismatch repair inactivation. By screening 18 loci for mutations, Pasqualucci et al. (2001) identified changes in the germline sequences of PIM1 (164960), MYC, ARHH (602037), and/or PAX5 (167414), in addition to BCL6, in a majority of diffuse large-cell lymphomas (DLCLs; see 601889). No mutations in PIM1, MYC, ARHH, and PAX5 were detected in germinal-center lymphocytes, naive B cells, or B-cell malignancies other than DLCLs. MYC mutations, which were found in 32% of DLCLs, were located downstream of the major P1/P2 promoters in exon 1 or downstream of the minor P3 promoter in exon 2. FISH analysis indicated that hypermutation in these genes is not due to chromosomal translocation, as seen in Burkitt lymphoma (113970). Chromosomal translocation, however, may be an outcome of hypermutation. Specific features of the hypermutation process, including the predominance of single nucleotide substitutions with occasional deletions or duplications, a preference for transitions over transversions, and a specific motif targeting RGYW, were recognizable in each of the hypermutated loci. Pasqualucci et al. (2001) proposed that aberrant hypermutation of regulatory and coding sequences of genes that do not represent physiologic targets may provide the basis for DLCL pathogenesis and explain its phenotypic and clinical heterogeneity. This hypermutation malfunction is unlikely to be due to defective DNA mismatch repair and does not appear to involve activation-induced deaminase (AICDA; 605257)

Trumpp et al. (2001) reported the generation of an allelic series of mice in which Myc expression is incrementally reduced to zero. Fibroblasts from these mice showed reduced proliferation, and after complete loss of Myc function they exited the cell cycle. Trumpp et al. (2001) showed that Myc activity is not needed for cellular growth but does determine the percentage of activated T cells that reenter the cell cycle. In vivo, reduction of Myc levels resulted in reduced body mass owing to multiorgan hypoplasia, in contrast to Drosophila dmyc mutants, which are smaller as a result of hypotrophy. Trumpp et al. (2001) found that dmyc substitutes for Myc in fibroblasts, indicating they have similar biologic activities. Trumpp et al. (2001) concluded that there may be fundamental differences in the mechanisms by which mammals and insects control body size, and proposed that in mammals MYC

controls the decision to divide or not to divide and thereby functions as a crucial mediator of signals that determine organ and body size.

Feng et al. (2002) showed that MYC physically interacts with SMAD2 (601366) and SMAD3 (603109), 2 specific signal transducers involved in TGF-beta (190180) signaling. Through its direct interaction with SMADs, MYC binds to the SP1 (189906)-SMAD complex on the promoter of the p15(INK4B) gene (600431), thereby inhibiting the TGF-beta-induced transcriptional activity of SP1 and SMAD/SP1-dependent transcription of the p15(INK4B) gene. The oncogenic MYC promotes cell growth and cancer development partly by inhibiting the growth inhibitory functions of SMADs.

To explore the role of MYC in carcinogenesis, Pelengaris et al. (2002) developed a reversible transgenic mouse model of pancreatic beta-cell oncogenesis using a switchable form of the MYC protein. Activation of MYC in adult, mature beta cells induced uniform beta-cell proliferation but was accompanied by overwhelming apoptosis that rapidly eroded beta-cell mass. Thus, the oncogenic potential of MYC in beta cells was masked by apoptosis. Upon suppression of MYC-induced beta-cell apoptosis by coexpression of BCLXL (600039), MYC triggered rapid and uniform progression into angiogenic, invasive tumors. Subsequent MYC deactivation induced rapid regression associated with vascular degeneration and beta-cell apoptosis. These data indicated that highly complex neoplastic lesions can be both induced and maintained in vivo by a simple combination of 2 interlocking molecular lesions.

Jain et al. (2002) used a conditional transgenic mouse model for MYC-induced tumorigenesis to demonstrate that brief inactivation of MYC results in the sustained regression of tumors and the differentiation of osteogenic sarcoma cells into mature osteocytes. Subsequent reactivation of MYC did not restore the cells' malignant properties but instead induced apoptosis. Thus, Jain et al. (2002) concluded that brief MYC inactivation appears to cause epigenetic changes in tumor cells that render them insensitive to MYC-induced tumorigenesis. The authors raised the possibility that transient inactivation of MYC may be an effective therapy for certain cancers.

To identify target genes of MYC, Menssen and Hermeking (2002) performed serial analysis of gene expression (SAGE) after adenoviral expression of MYC in primary human umbilical vein endothelial cells. Induction of 53 genes was confirmed using microarray analysis and quanitative real-time PCR. Among these genes was MetAP2, also called p67 (601870), which encodes an activator of translational initiation and represents a validated target for inhibition of neovascularization. Furthermore, MYC induced 3 cell cycle regulatory genes and 3 DNA repair genes, suggesting that MYC couples DNA replication to processes preserving the integrity of the genome. MNT (603039), a MAX-binding antagonist of MYC function, was upregulated, implying a negative feedback loop. In vivo promoter occupancy by MYC was detected by chromatin immunoprecipitation for at least 5 genes, showing that they are direct MYC targets. The authors suggested that the MYC-regulated genes identified by this study define a set of bonafide MYC targets and may have potential therapeutic value for inhibition of cancer cell proliferation, tumor vascularization, and restenosis.

Leven (2002) discussed and diagrammed the complex web of MYC-related pathways involved in growth, proliferation, and apoptosis.

Vafa et al. (2002) showed that brief MYC activation can induce DNA damage prior to S phase in normal human fibroblasts. Damage correlated with induction of reactive oxygen species (ROS) without induction of apoptosis. Deregulated MYC partially disabled the p53-mediated DNA damage response, enabling cells with damaged genomes to enter the cycle, resulting in poor clonogenic survival. An

antioxidant reduced ROS, decreased DNA damage and p53 activation, and improved survival. The authors proposed that oncogene activation can induce DNA damage and override damage controls, thereby accelerating tumor progression via genetic instability.

ALLELIC VARIANTS
(selected examples)

.0001 BURKITT LYMPHOMA [MYC, PRO57SER]

Bhatia et al. (1993) found homozygosity for a CCC-to-TCC transition converting proline-57 to serine in Burkitt lymphoma-20 (DIF).

.0002 BURKITT LYMPHOMA [MYC, ASN86THR]

Bhatia et al. (1993) found homozygosity for an AAC-to-ACC transition converting asparagine-86 to threonine in Burkitt lymphoma-21 (DS179).

.0003 BURKITT LYMPHOMA [MYC, GLU39ASP]

Bhatia et al. (1993) found homozygosity for a GAG-to-GAC transversion converting glutamic acid-39 to to aspartic acid in Burkitt lymphoma-25 (JLP).

.0004 BURKITT LYMPHOMA [MYC, PRO59ALA]

Bhatia et al. (1993) found homozygosity for a CCG to GCG transversion converting proline-59 to alanine in Burkitt lymphoma-30 (WMN).

SEE ALSO

Battey et al. (1983); Beimling et al. (1985); Bernard et al. (1983); Colby et al. (1983); Dalla-Favera et al. (1982); Dunnick et al. (1983); Erikson et al. (1983); Hamlyn and Rabbitts (1983); Hayday et al. (1984); Magrath et al. (1983); Marcu et al. (1983); Murphy et al. (1986); Neel et al. (1982); Persson et al. (1984); Peschle et al. (1984); Saito et al. (1983); Sakaguchi et al. (1983); Watt et al. (1983); Watt et al. (1983)

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